S. HRG. 103–1056

MEDICINES FOR DRUG ABUSE: REVIEWING THE STRATEGY

Y 4. J 89/2: S. HRG. 103-1056

Medicines for Drug Abuse: Reviewing...

HEARING

BEFORE THE

COMMITTEE ON THE JUDICIARY
UNITED STATES SENATE

ONE HUNDRED THIRD CONGRESS

SECOND SESSION

ON

FOCUSING ON THE RESEARCH AND DEVELOPMENT OF MEDICINES, CALLED PHARMACOTHERAPIES, TO TREAT DRUG ADDICTION

APRIL 19, 1994

Serial No. J–103–51

Printed for the use of the Committee on the Judiciary

SUPERINTENDENT OF DOCUMENTS
DEPOSITORY
NOV 1 4 1995
BOSTON PUBLIC LIBRARY
GOVERNMENT DOCUMENTS DEPT

U.S. GOVERNMENT PRINTING OFFICE
91–890 CC WASHINGTON : 1995

For sale by the U.S. Government Printing Office
Superintendent of Documents, Congressional Sales Office, Washington, DC 20402
ISBN 0-16-047671-2

S. HRG. 103–1056

MEDICINES FOR DRUG ABUSE: REVIEWING THE STRATEGY

4. J 89/2: S. HRG. 103-1056

edicines for Drug Abuse: Reviewing...

HEARING

BEFORE THE

COMMITTEE ON THE JUDICIARY
UNITED STATES SENATE

ONE HUNDRED THIRD CONGRESS

SECOND SESSION

ON

FOCUSING ON THE RESEARCH AND DEVELOPMENT OF MEDICINES, CALLED PHARMACOTHERAPIES, TO TREAT DRUG ADDICTION

APRIL 19, 1994

Serial No. J–103–51

Printed for the use of the Committee on the Judiciary

SUPERINTENDENT OF DOCUMENTS
DEPOSITORY
NOV 1 4 1995
BOSTON PUBLIC LIBRARY
GOVERNMENT DOCUMENTS DEPT

U.S. GOVERNMENT PRINTING OFFICE
91–890 CC WASHINGTON : 1995

For sale by the U.S. Government Printing Office
Superintendent of Documents, Congressional Sales Office, Washington, DC 20402
ISBN 0-16-047671-2

COMMITTEE ON THE JUDICIARY

JOSEPH R. BIDEN, JR., Delaware, *Chairman*

EDWARD M. KENNEDY, Massachusetts
HOWARD M. METZENBAUM, Ohio
DENNIS DECONCINI, Arizona
PATRICK J. LEAHY, Vermont
HOWELL HEFLIN, Alabama
PAUL SIMON, Illinois
HERBERT KOHL, Wisconsin
DIANNE FEINSTEIN, California
CAROL MOSELEY-BRAUN, Illinois

ORRIN G. HATCH, Utah
STROM THURMOND, South Carolina
ALAN K. SIMPSON, Wyoming
CHARLES E. GRASSLEY, Iowa
ARLEN SPECTER, Pennsylvania
HANK BROWN, Colorado
WILLIAM S. COHEN, Maine
LARRY PRESSLER, South Dakota

CYNTHIA C. HOGAN, *Chief Counsel*
CATHERINE M. RUSSELL, *Staff Director*
MARK R. DISLER, *Minority Staff Director*
SHARON PROST, *Minority Chief Counsel*

CONTENTS

STATEMENTS OF COMMITTEE MEMBERS

	Page
Biden, Hon. Joseph R., Jr., U.S. Senator from the State of Delaware	1
Hatch, Hon. Orrin G., U.S. Senator from the State of Utah	2

CHRONOLOGICAL LIST OF WITNESSES

Panel consisting of Laurence E. Earley, senior associate dean and Francis C. Wood, professor of medicine, University of Pennsylvania, Philadelphia, PA; accompanied by Herbert D. Kleber, executive vice president and medical director, Center on Addiction and Substance Abuse, and professor of psychiatry, Columbia University College of Physicians and Surgeons, New York, NY; Charles O'Brien, chief of psychiatry, Philadelphia Veterans Affairs Medical Center, and professor and vice chair of psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA; and J. Richard Crout, former vice president of Medical and Scientific Affairs Boehringer Mannheim Pharmaceuticals Corp., and scholar-in-residence, Institute of Medicine, Washington, DC	5

ALPHABETICAL LIST AND MATERIAL SUBMITTED

Biden, Hon. Joseph R., Jr.: Testimony	1
Crout, J. Richard: Testimony	15
Earley, Laurence E.:	
Testimony	5
Prepared statement	7
Hatch, Hon. Orrin G.: Testimony	2
Kleber, Herbert D.: Testimony	18
O'Brien, Charles: Testimony	9

MEDICINES FOR DRUG ABUSE: REVIEWING THE STRATEGY

TUESDAY, APRIL 19, 1994

U.S. SENATE,
COMMITTEE ON THE JUDICIARY,
Washington, DC.

The committee met, pursuant to notice, at 10:08 a.m. in Room SD–226, Dirksen Senate Office Building, Hon. Joseph R. Biden, Jr., (chairman of the committee), presiding.

Also present: Senator Hatch.

OPENING STATEMENT OF HON. JOSEPH R. BIDEN, JR., A U.S. SENATOR FROM THE STATE OF DELAWARE

The CHAIRMAN. The hearing will come to order, please. I welcome this esteemed panel. It is rare we have people of such accomplishment before this committee, or any committee, and I know how incredibly busy you all are. I truly appreciate your willingness to be here today and all the work you have done.

I have an opening statement. I don't want to take too much of the committee's time and of the witnesses' time, but I feel it is important to sort of put this in context and the reason why I feel so strongly about the need to have this hearing.

Today, the Judiciary Committee continues its oversight of the national drug strategy with a review of one of the Nation's boldest scientific attempts—the research and development of medicines, called pharmacotherapies, to treat drug addiction.

Nearly 5 years ago, in December 1989, I released a Judiciary Committee report, "Pharmacotherapy: A Strategy for the 1990's." In this report, I argued that there was scientific promise for medicines that might lessen an addict's craving for cocaine, or that might even block the impact of cocaine on the addict's brain. This report asked the question, "If drug abuse is an epidemic, are we doing enough to find a medical cure?"

At the time, despite the efforts of myself and others in the Congress, including Senators Kennedy and Moynihan, as well as late Representative Silvio Conte, the answer to that question was as clear as it was distressing. The Nation was doing far too little to find medicines that treat the disease of drug addiction.

To address this shortfall, I authored, along with Senator Kennedy, the Pharmacotherapy Development Act, which passed into law in 1992. The cornerstone of this act was its call for a 10-year $1 billion effort to research and develop antiaddiction medications, and because the science was in such early stages, this legislation also called on the world renowned National Academy of Sciences to

review the research and to offer their recommendations. Was this research real or was it science fiction?

Today, the committee will hear the answer from four of the Nation's leading medical scientists who authored this most recent and most complete report ever undertaken on the research and development of antiaddiction medications. With the help of the other distinguished scientists on the Research Committee and the staff of the National Academy of Sciences' Institute of Medicine, this report offers a hopeful answer and a sensible road map.

The hopeful answer is that there is a real and profound promise that medications to treat the mystery of cocaine addiction can be discovered, mirroring the success with medications for heroin addiction. Are these medications magic bullets? Well, the answer is clearly no, they are not, but such medications, if developed, would be a vital partner with the drug treatments that we have today.

The sensible road map charted by the Institute of Medicine report calls for, first, full funding for the Medications Development Division; second, an end to the tangle of regulations that can hamstring this research effort; and, third, a recognition that the pharmaceutical industry can, should, and indeed must be a partner in the effort to deliver medicines to the millions suffering from drug addiction.

I cannot think of another disease that directly threatens the 6 million Americans who are hard-core addicts, trapped by the perverse chemistry of illegal drugs, and that indirectly threatens tens of millions of other Americans for which we would hesitate to unleash the full powers of America's unparalleled medical science community.

We have already delayed too long. The most august scientific body in the world has outlined concrete steps for developing new antiaddiction therapies. I would hope that today would be the first day we move toward the potential promise just over the horizon, or I fear tomorrow will turn into next year, and then the next century, and too many Americans will become and remain addicts or the victims of addicts, the victims of crimes, as a consequence of addiction.

If we have the boldness and the wisdom to focus on the future, on finding new and better answers to treating drug addiction, I am confident that the powerful grip of illegal drugs over so many Americans can and will end.

I would now yield to my colleague from Utah before I move to the witnesses and introduce the witnesses.

Senator Hatch?

STATEMENT OF HON. ORRIN G. HATCH, A U.S. SENATOR FROM THE STATE OF UTAH

Senator HATCH. Well, thank you, Mr. Chairman. I am happy to be with you here today, and I do think these are very important hearings, in this very interesting area of the law and of science.

I want to welcome our distinguished panel here today, and I look forward to their presentation. I won't be able to stay throughout because I have five committee conflicts at the same time, one of which is in the Finance Committee which I have to attend. So I

apologize for that, but I am very interested in what you have to say in this area.

I commend the chairman for bringing this issue to our attention because I think it is important that we review all possible weapons in the war against drugs, and continue to build on the progress of the past two administrations, and hopefully to reverse the alarming upswings in drug use that recently we have found are occurring—especially among our young people.

As the panel members have noted in their report, the use of antiaddictive medicines as a method of treating drug addiction has received relatively scant attention in recent years, perhaps too little attention. The report also states that this method of treatment has not received widespread support from the Federal Government, nor has the private sector been active in either the development of or promotion of antiaddiction medications.

Many Americans, I believe, instinctively know that the problems associated with drug-using behaviors and drug addiction itself are complicated processes which do not respond simply to one particular intervention or approach. There has been a great deal of focus in treatment research on nonpharmacological therapies, such as counseling, behavioral interventions, contingency management, psychotherapy, relapse prevention, and community therapies. In reviewing all of our options for reducing drug abuse, I believe that it is important that we take a focused look at medications developed under various programs, including those at the National Institute on Drug Abuse.

So I welcome the opportunity to explore some of these issues and the benefits that this method of fighting drug abuse might offer, as well as the various costs involved in pursuing those particular benefits. As I have said on more than one occasion, I believe that treatment is an important weapon in the drug war, but I believe we need to review carefully our treatment options and choose those most appropriate and with the greatest chance of success so that our scarce treatment monies will be well spent.

Having worked with addicted people and drug abusers before I came here and since I have come here, I have to say it is a very, very difficult set of problems and there are no simple solutions. So I personally appreciate the members of this panel and the efforts that they have put forth and the work that all of you have done to try and solve some of these problems, and I look forward to hearing your expert testimony here today.

I want to thank you again, Mr. Chairman, for holding these hearings.

The CHAIRMAN. Thank you, Senator. As you gentlemen know, Senator Hatch has a dual responsibility and, on this particular issue, has a good deal of influence. He is also a major player, and was the ranking member of the Labor Committee, which has jurisdiction over this issue, the health side of it. So he is one of the target group whom I am aiming this effort at, and I must tell you this report that you all have issued is a very—I know there is going to be a second followup at the end of the year, but this is a very important document.

Let me introduce you all for the record, if I may. Our first witness is Dr. Laurence Earley, the senior associate dean and director

of the Office of International Medical Programs at the University of Pennsylvania Medical Center. Dr. Earley is currently the Francis C. Wood professor of Medicine at the University of Pennsylvania, a position he has held since 1983. Prior to his tenure at Penn, Dr. Earley taught at three of the Nation's finest medical schools—Harvard University, the University of California at San Francisco, and the University of Texas Health Sciences Center in San Antonio. Dr. Earley is chairman of the committee to Study Medications Development at the Institute of Medicine of the National Academy of Sciences, the committee that oversaw the report we will review today.

Dr. Charles O'Brien is currently chief of psychiatry at the Philadelphia Veterans Affairs Medical Center, and professor and vice chairman of psychiatry at the University of Pennsylvania. Dr. O'Brien is also director of the University of Pennsylvania's Addiction Research Center, and I have had the great pleasure and privilege of spending a little, far too little, time with him up on campus as he showed me through some of the programs that they are working on.

Dr. O'Brien has authored more than 260 publications on addictive disorders and biological psychiatry, and conducted research on the pharmacotherapy of addiction and the development of new behavioral and pharmacological treatments for addiction. In 1991, he was elected to the Institute of Medicine of the National Academy of Sciences. As all of our witnesses today, Dr. O'Brien is a member of the committee to Study Medications Development and Research.

Dr. Richard Crout recently retired after 10 years service as the vice president for Medicine and Scientific Affairs at Boehringer Mannheim Pharmaceuticals Corporation. Prior to his work in the pharmaceutical industry, Dr. Crout served as assistant surgeon general from 1976 to 1984, and directed the Bureau of Drugs at the Food and Drug Administration from 1973 to 1992. He also taught at the University of Texas Southwestern Medical School and Michigan State University. Today, as the rest of our distinguished panel, he is an institute of medicine scholar-in-residence, and I welcome him as well.

An old friend who will be here whom we have worked with a good deal of the time, the fourth member of the panel, cannot be here because of a conflict in time commitment. We will hear testimony from Dr. Kleber when he arrives, but for the record Dr. Kleber, since November 1991, has been the executive vice president and medical director of the Center on Addiction and Substance Abuse at Columbia University. Prior to this, he served for 2 years as the deputy director for demand reduction at the Office of National Drug Control Policy under Director William Bennett and was always a very informative and very helpful witness before this committee. Before joining the government, Dr. Kleber was a professor of psychiatry at Yale University and the director of the Substance Abuse Treatment Unit at the Connecticut Mental Health Center.

So I welcome you all and look forward to Dr. Kleber coming by. Again, I cannot thank you enough for the wonderful work you have done, and I sincerely hope that the result of this and the followon report will be to engage this Nation in a more earnest and urgent effort to deal with the things that you are going to speak to today.

With that, why don't I yield the floor to you, Mr. Chairman, and then we will move on.

PANEL CONSISTING OF LAURENCE E. EARLEY, SENIOR ASSOCIATE DEAN AND FRANCIS C. WOOD, PROFESSOR OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA; ACCOMPANIED BY HERBERT D. KLEBER, EXECUTIVE VICE PRESIDENT AND MEDICAL DIRECTOR, CENTER ON ADDICTION AND SUBSTANCE ABUSE, AND PROFESSOR OF PSYCHIATRY, COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS, NEW YORK, NY; CHARLES O'BRIEN, CHIEF OF PSYCHIATRY, PHILADELPHIA VETERANS AFFAIRS MEDICAL CENTER, AND PROFESSOR AND VICE CHAIR OF PSYCHIATRY, UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE, PHILADELPHIA, PA; AND J. RICHARD CROUT, FORMER VICE PRESIDENT OF MEDICAL AND SCIENTIFIC AFFAIRS, BOEHRINGER MANNHEIM PHARMACEUTICALS CORP., AND SCHOLAR-IN-RESIDENCE, INSTITUTE OF MEDICINE, WASHINGTON, DC

STATEMENT OF LAURENCE E. EARLEY

Dr. EARLEY. Thank you, Senator Biden and Senator Hatch. Let me say that we are very pleased to have the opportunity to be here before you today to discuss this report. I might also add that your very accurate introductions of the members of our committee has used up about half of my introductory remarks.

I would like to recognize two other members of the committee, Dr. Joan Culpepper-Morgan from Yale and Dr. Albert Williams from the RAND Corp., who are also with us.

The CHAIRMAN. Welcome, and thank you both as well. Thank you for being here.

Dr. EARLEY. I would also like to recognize the very able members of the Institute of Medicine staff who have put so much effort into this study and into the generation of this report—Dr. Constance Pechura, associate director of the Board of Behavioral Sciences and Mental Disorders; Carolyn Fulco, the study director; Cathryn Liverman, a research associate; and Terri Barba, an assistant, all of whom are with us this morning.

The CHAIRMAN. I welcome you, also. Thank you again for participating in this and, as I said, I look forward to the second half of this report as well.

Dr. EARLEY. As you have pointed out, the committee was mandated by the Alcohol, Drug Abuse and Mental Health Reorganization Act of July 1992 and was charged to examine several issues, including the extent to which current scientific knowledge limits the development of antiaddictive medications, the activity and accomplishments of the Medications Development Division of the National Institute on Drug Abuse since its inception in 1990, the role of the FDA and other regulatory agencies in the process of approving antiaddictive, and the current role of the private sector in the discovery and development of antiaddictive medications and the incentives and disincentives in this area.

Our full committee met three times, beginning in October 1993, and submitted its first report, which you have before you, last

month. We will reconvene again this afternoon, and we expect to present a second report in December 1994.

We met with senior representatives of the pharmaceutical industry and the relevant government agencies, and in addition to considering relevant scientific and other data, a service of the pharmaceutical and biotechnology industry was conducted. The committee concluded that pharmacotherapy potentially can be an effective means of treating drug addiction, especially in conjunction with other kinds of treatment and supportive and educational approaches.

Despite the recognized success of methadone and the promise of the longer-acting agent LAAM in the treatment of heroin addiction, there have been no new medications discovered since the late 1960's and early 1970's. There is no specific medication for the treatment of cocaine addiction. Our report emphasizes that this lack of activity persists despite the growing socioeconomic, criminal and primary and secondary health problems associated with illicit drug use.

As a committee, we believe that many of the reasons for lack of activity in the discovery and development of antiaddictive medications can be identified, and although solutions to the problems are not easy or simple, potentially effective approaches can be devised.

In a very general sense, the problematic areas include limited scientific understanding of the physiologic basis of addiction, craving and relapse; failure to identify pharmacotherapeutic research as a national priority in the "war on drugs"; and deterrence to research and development in either the academic and private sectors, including limited goal-directed funding, lack of national priority, regulatory impediments, both Federal and State, to the clinical research, review and approval, payment for care and medications, product liability, and recovery of investment.

These problems have understandably limited the extent to which the Medications Development Division of the National Institute on Drug Abuse has been able to stimulate the development of new medications. However, the committee has taken note of the role the division played in bringing together the Food and Drug Administration and the Drug Enforcement Administration to expedite the review and approval for use of the long-acting medication LAAM.

In the present report, the committee makes specific recommendations that address aspects of these general problematic areas, and additional recommendations will be included in our second report. We are recommending that the need for research and development of antiaddictive medications be articulated at the highest level of government, clearly to the public to involve governmental agencies, to the academic community, and to industry.

We are recommending that new funding be identified for the purpose of establishing comprehensive centers for the study of drug addiction. These centers would encompass basic research, clinical research, treatment, and training. We are recommending that the National Institute on Drug Abuse reexamine its internal organization for the review and support of basic and clinical research, with a view toward establishing institute-wide goals and procedures.

We hope that this report will bring renewed attention to pharmacotherapy as a promising modality for treating drug addic-

tion and that the report will be useful not only to the National Institute on Drug Abuse and the Executive Branch, but also to you as legislative options for dealing with drug addiction are considered and priorities are set.

Mr. Chairman and Senator Hatch, this concludes my introductory remarks. My colleagues and I will be pleased to respond to your questions and to elaborate on any points I have made thus far.

[Prepared statement of Laurence Earley follows:]

PREPARED STATEMENT OF LAURENCE EARLEY, M.D.

Mr. Chairman and members of the Committee, my name is Laurence Earley and I am pleased to come before you as Chairman of the Institute of Medicine Committee to Study Medication Development and Research at the National Institute on Drug Abuse (NIDA). In addition to chairing this Institute of Medicine (IOM) committee, I am Senior Associate Dean and the Francis C. Wood Professor of Medicine at the University of Pennsylvania. Accompanying me today are several members of the IOM committee: Dr. J. Richard Crout, former Vice President for Medical and Scientific Affairs at Boehringer Mannheim Pharmaceuticals Corporation; Dr. Herbert D. Kleber, Executive Vice President and Medical Director of the Center on Addiction and Substance Abuse, and Professor of Psychiatry at Columbia University College of Physicians and Surgeons; and Dr. Charles P. O'Brien, Chief of Psychiatry, Philadelphia Veterans Affairs Medical Center, and Professor and Vice-Chair of Psychiatry at the University of Pennsylvania School of Medicine. In addition to the committee members, with us are members of the IOM staff who worked on this project: Dr. Constance Pechura, Associate Director of the Board on Biobehavioral Sciences and Mental Disorders, Carolyn Fulco, Study Director, and Catharyn Liverman, Research Associate.

As you know, the ADAMHA Reorganization Act of July 1992 (Public Law 102–321) stipulated that the Department of Health and Human Services contract with the National Academy of Sciences to establish a committee to examine the current situation in and incentives and disincentives for the development of anti-addiction medications. In response to the Congressional mandate, the Committee to Study Medication Development and Research at the National Institute on Drug Abuse was formed by the Institute of Medicine: it held its first meeting in October 1993 and delivered its report to NIDA on March 15 just prior to the Senate Appropriation Hearings for the National Institutes of Health on March 17.

The committee was charged to examine several issues, including:

- The extent to which current scientific knowledge limits the development of pharmacological treatments for drug addiction;
- The background and progress of NIDA's Medications Development Division (MDD) since its inception in 1990;
- The current role of the Food and Drug Administration (FDA) and other government entities in the process for approving anti-addiction medications;
- The incentives and disincentives to private development of medications including government regulatory processes and the potential market for anti-addiction medications; and
- The current role of the private sector in the development of medications for drug addiction.

The committee notes that pharmacotherapy as an approach to treating drug addiction has received far too little attention, despite the clinical success of methadone, which dates back to the 1960s. Over the last 30 years only two additional medications have been approved for the treatment of opiate addiction, naltrexone and levo-alpha-acetylmethadol, known by the acronym LAAM and it is important to note that both of these medications were developed in the 1960s and early 1970s. There is no approved medication for the treatment of cocaine addiction. During the same 30 year period, serious medical and social problems have evolved as drug addiction has become a route for spreading AIDS through the sharing of contaminated needles and trading sex for drugs, multiple-drug-resistant tuberculosis has become common in immunocompromised HIV-infected drug addicts, an association between illicit drug use and increasing violent crime is clear, and the medical consequences for infants of in utero exposures to cocaine have become evident.

Current estimates place the number of cocaine addicts at 2.1 million and the number of heroin addicts at 0.5 million to 1 million. Given the magnitude of the illicit drug-use problem and its effects on the economy and public health, the committee strongly believes that addressing this issue requires a dedicated effort, not only to develop pharmacotherapies, but also to foster prevention, education, and the use of other treatment approaches. Pharmacotherapy is one type of treatment and is potentially a viable adjunct to other treatment types, yet the development of pharmacotherapy has not received widespread support from the federal government, and the private sector has been relatively inactive in developing anti-addiction medications.

It was in a climate of a near absence of private sector and government activity in the development of anti-addiction medications that Congress passed P.L. 100–690 in 1988, which established the Medications Development Division in the National Institute on Drug Abuse. The division began in 1990 to coordinate and encourage academic, private, and federal regulatory involvement in developing and bringing to market new medications for the treatment of drug addiction. The MDD has had a modest degree of success over the past three years, most notably in bringing LAAM to market. However, it quickly became evident to the committee that development of anti-addiction medications requires federal commitment and leadership from the executive branch of government, and the overcoming of a variety of scientific, marketing and regulatory hurdles. The major disincentives cited by the pharmaceutical industry, and supported by the committee, include:

(1) The inadequate scientific understanding of addiction and how to prevent relapse;

(2) The lack of aggressive federal commitment and leadership;

(3) An uncertain market environment, which involves issues such as FDA and Drug Enforcement Administration (DEA) regulations;

(4) The size of the market;

(5) Pricing of medications;

(6) Reimbursement by federal and other third party payors;

(7) Liability;

(8) And difficulties encountered in conducting clinical research.

In evaluating these issues, the committee recommends ways to overcome some of the disincentives noted above and will provide additional recommendations for policy and legislative options in our second report, which we expect to submit in December of this year. It is the strong belief of the committee, however, that unless basic research is supported at an appropriate funding level, it will be difficult to accumulate the scientific knowledge base necessary for the private sector and the MDD to develop new and perhaps novel anti-addiction medications. Additionally, the committee believes that the paucity of basic knowledge is best approached through a nationally coordinated effort, and recommends that NIDA designate national drug abuse research centers, supported by new congressional appropriations, as described in the ADAMHA Reorganization Act [Public Law 102–321, Section 464N (a)]. The committee recommends that such centers encompass all aspects of drug-abuse research. The committee believes that the creation of such centers would result in progress in basic and clinical research, and in the treatment of drug addiction.

In its report, the Institute of Medicine committee also makes several recommendations to NIDA for developing a strategy to work with industry and for improving programs within the MDD and I refer you to the report for the specifics of those recommendations. The committee noted that development of anti-addiction medications depends critically on cooperation between the public and private sectors. Yet, the number of federal agencies involved, agency funding and staffing levels, and regulatory requirements pose difficult challenges to successful cooperation. With regard to regulatory issues, the committee provides several recommendations aimed at overcoming barriers, particularly exempting clinical researchers from the reporting requirements of the Drug Enforcement Administration that duplicate the oversight activities of the Food and Drug Administration; several alternative policy options are also provided.

Finally, government policies clearly have not provided the environment for anti-addiction medication development nor has there been a strong emphasis on the use of pharmacotherapy in the treatment of drug addiction. This inadequate federal leadership represents an additional disincentive to industry, in that it affects the involved agencies' abilities to establish clear guidelines, enhance interagency cooperation, and provide research programs with the stability necessary for medica-

tion discovery and development. The committee believes that explicit action by the President, such as issuing an executive order assigning a high priority to the development of medications for drug-abuse treatment could enhance cooperation among government agencies involved in this area, would focus their activities, and lessen or eliminate existing institutional barriers. Such high level action would have the added benefit of signaling to the private sector that the development of anti-addiction medications is a matter of high national priority.

For your information, the 14-member interdisciplinary IOM committee included persons with expertise in behavioral pharmacology, drug treatment, neuroscience, drug development health-care economics, clinical research, and federal regulatory law. The full committee met three times and there were several subcommittee meetings. The committee reviewed the relevant scientific literature, evaluated NIDA documents, met with senior executives of pharmaceutical companies and representatives of federal agencies (the DEA, NIDA, NIH, and FDA), and met with the IOM Forum on Drug Development. Additionally, a survey of the member companies of Pharmaceutical Manufacturers Association, the Biotechnology Industry Organization, and the Generic Pharmaceutical Industry Association was conducted.

This is the first of two reports to be issued by the committee. As previously mentioned, this first report examines the climate for development of anti-addiction medications. The second report will recommend policy and legislative proposals intended to stimulate private involvement in this field by overcoming some of the disincentives, many of which are identified in the first report.

The committee focused its attention on medications for treating opiate and cocaine addictions, although it recognized that the two addictive drugs that are most important with respect to morbidity, mortality, and economic costs are alcohol and nicotine. Those two legal substances are not in the purview of the NIDA MDD. However, the IOM Committee on Preventing Nicotine Dependency in Children and Youths will issue its report in the fall of 1994.

Mr. Chairman and members of the committee, we hope that this report, and the one to follow, will focus renewed attention on pharmacotherapy as a valid and promising mode of drug treatment and that the report will be useful not only to the National Institute on Drug Abuse and to the executive branch, but also to you, as legislative options for treating drug addiction are examined and priorities are set.

We are happy to answer any questions you or members of this distinguished committee may have. Thank you.

The CHAIRMAN. Thank you, doctor. I would like to ask a couple of overview questions. The Institute of Medicine report that you have submitted points out that we know a great deal about how opiates work, particularly heroin—how they work in the brain and the mechanisms of action that take place. It is this knowledge that has made the development of methadone, which now treats about 100,000 heroin addicts, and LAAM possible.

Now, could you give the committee, any one of you or all of you, or however you wish to proceed, an overview on what we know about the mechanisms of cocaine and how they work in the brain? It would be a useful thing if you could.

Dr. EARLEY. I would prefer, Mr. Chairman, to defer perhaps to Dr. O'Brien first to respond to that question.

The CHAIRMAN. Fine. Doctor, the floor is yours.

STATEMENT OF CHARLES O'BRIEN

Dr. O'BRIEN. Mr. Chairman, we are actually living in a time of an explosion of knowledge about the brain. This is actually the decade of the brain, and based on what neuroscience has taught us about how our brain works, we have learned, in consort with this, a tremendous amount about how cocaine works.

It turns out that cocaine pretty much has a direct line to the pleasure centers in the brain. These systems are the same systems that are turned on by a good meal, by a symphony, by a good snow if you are a skier. These systems, though, can be kind of short-circuited by drugs, and it turns out that all of the drugs that both

animals will avidly take and humans will take in an addictive way act on these centers to give you this pleasure without having to work for it. This is one of the pernicious aspects of drug abuse because people from a very early age who take these drugs can get euphoria, can get high; the same kind of thing that you might have to work very hard to get in a normal, natural way, they can get it very intensively.

Now, different drugs, like heroin, nicotine, marijuana and alcohol, activate this system in different ways. Cocaine is probably the most direct and most intense because cocaine acts on the neurotransmitter, the major chemical involved in this system, and it acts to make much more of this chemical, called dopamine, available.

It does this, actually—and I could get up and give you the details, but this cartoon over there describes a simple dopamine receptor in this pleasure pathway in the brain. What cocaine does is block the reuptake mechanism. The brain is set up so that everything is conserved; it is used over and over again. But when cocaine is present, and this happens within seconds of a dose of cocaine, this reuptake mechanism is blocked, so more dopamine is available than ever before and the person feels an intense surge of pleasure.

The CHAIRMAN. The presence of dopamine is what creates the feeling of pleasure, is that correct?

Dr. O'BRIEN. Yes, sir, that is a simplified way of saying it because there are neurotransmitters as well, but dopamine, as far as we know, is the major one.

The CHAIRMAN. I am sorry to interrupt.

Dr. O'BRIEN. Well, that is the way that we believe that cocaine gives this intense feeling of pleasure. Now, what is particularly bad about cocaine is that it sets up a habit. It facilitates itself, so that with repeated use the person begins to get euphoria from cocaine even before they take the cocaine into their body. There is a learning process, a sensitization process that goes on, and this is what makes it so difficult to treat because even when a person stops taking cocaine, this memory effect continues. It can go on for months, perhaps even years, after the last dose of cocaine, which makes a person very prone to relapse even when you have gotten them to stop taking it for a while.

The CHAIRMAN. Maybe you could distinguish for me, if you can, what the difference is between the mechanism of action in the brain with the consumption of cocaine, which you have just done, and heroin or an opiate.

Dr. O'BRIEN. Well, heroin acts directly on opiate receptors which are involved in this pathway as well to modulate the effects of dopamine through different mechanisms, not through this reuptake mechanism that I described. But the net result of heroin is also to increase dopamine. The same is true of alcohol, the same is true of nicotine. These centers are activated by these drugs.

The CHAIRMAN. I am going to ask you some overly-simplistic questions for the record, some of which you have already educated me to prior to this hearing. But the thing that I find that is the hardest when I am attempting as a nonscientist to make policy or influence policy that would call on the American people and their

elected representatives to invest more of their tax dollars in seeking pharmacotherapy, not solutions, but pharmacotherapy regimes that would help in treatment, it is very difficult for people to understand how any of this works.

They think in terms of taking a pill that stops you from sneezing or taking a pill for dealing with an infection or taking a pill or a shot that causes a particular reaction in the body. Although they don't understand that in any detail, it is very difficult for people to understand, first—and I apologize for the editorializing here, and I know you run into this as well when you treat patients and their families because you deal with a holistic approach, not just this.

This, in effect, is a disease of the brain. I think the hardest thing I have found in dealing with the whole question of drug abuse in American society is that it is the one place where I find that people demand a success rate higher than in any other area.

If we said, for example, with regard to public education that no public school would be funded unless 95 percent of those who entered school in first grade graduated within 12 years, literally every public school, I think—I may be mistaken, but I think every public school—clearly, 98 percent of the public schools in America would be shut down. If we said 90 percent, we would shut them down. If we said 80 percent, we would shut the majority down.

Yet, when we go out to try to make the case for investment in treatment regimes to deal with the 6 million addicts who are committing 135 or 140 crimes a year to maintain their habit, on average, which is part of the 5.7 million crimes committed out there on a yearly basis that has America up in arms, with good reason, people look at me and say, basically, the following. It took me a long while to reach this conclusion.

They do not believe, nor is there overwhelming evidence to show, that we will be able to, "cure" the vast majority of people who are treated. Second, even if we were, I get the following response from people, and I am paraphrasing it: Senator, Charlie or Mary chose of their own free will to take this drug; they consciously broke the law; they received pleasure from breaking the law; they then, in turn, victimized me; they robbed my home, they beat up my child, they acted in an antisocial way, they murdered someone, they shot someone, and they generated this drug trade, because they are customers, in my neighborhood, and now you want me to pay more tax dollars to go out there and, "cure" that person who, in fact, has victimized me from the beginning and chose to get engaged in this of their own free will.

Notwithstanding that they fully understand the connection between addiction and crime and between the drug trade and crime, it bothers them, understandably, that they would have to spend money, as a byproduct of dealing with this problem, to help cure the person who did these bad things to them.

I apologize for that incredibly long preamble, but that is why I think it is important that people in my position provide forums for people in your position to explain to the American public that there is a chemical reaction that takes place in the brain that I think I am correct in saying—this is a question; I guess I should put it as a question—that no individual is able to, based on their free will,

say now that I have consumed this, I am not going to let it affect me. There is a chemical reaction that takes place, is that correct?

Dr. O'BRIEN. That is correct, sir.

The CHAIRMAN. And what these pharmacotherapies are attempting to do is not find a silver bullet, but provide some help to the medical profession and the treatment professionals to give this person a better opportunity to be able to avoid continuing to consume the drug that causes in many cases severe antisocial behavior, jeopardizing the safety of the American people.

There are young students back here who walk in and out of this room who are students that are part of the Close-Up Program, a nationwide program, and other programs. This is my last question and then I will yield to my colleague. How would you explain to them what takes place in their brain when they take cocaine, when they consume cocaine? They are obviously very intelligent young people, but they are young people. How do you explain it to them, not to your colleagues?

Can you say it, as they say—they used to say the newspapers should write at an eighth grade level. I think they write these days, present company excluded, at about a second grade level in terms of content sometimes because we speak in first grade terms, we who are public officials. But the truth is that they say, write at a level that the average person out there can understand it.

Try to explain for the record, because I am looking for something I can use when I speak to people, what the physiological reaction is, if that is the proper terminology is, in the brain when cocaine is consumed. You did it once. In as much layman's terms as I think you can muster, try it one more time in even more basic terms so those kids as they walk out of the room say, I know what Dr. O'Brien means.

Dr. O'BRIEN. Mr. Chairman, the first issue that you raised that is very important, though, is the one about free will and voluntarily deciding to do it because that is true. People first have to take it in the first place, and it would actually be better if they never even tried it because we know that some people have a built-in, genetically determined propensity to become addicted to various drugs. There is a family history aspect.

Crack cocaine in Philadelphia sells for as little as $2 a dose. I have seen in the New York Times that it sells for as little as $0.75 a dose in Manhattan. So it is so widely available that a lot of kids use it before they know what they are doing. So the first thing I would say is don't try it at all. Even though many people who try it seem to get away with it, you don't know if you are going to be the one who loses control.

The reason that people lose control is that this gives the user intense pleasure briefly and quickly at a cheap price; it may only be a couple of dollars. But then after this brief period of pleasure, there is a feeling of dysphoria or unhappiness and craving for more, so that you never really seem to get enough. Those people who become addicted actually end up spending their whole lives trying to get the drug and they have completely lost control of taking it because of this very intense effect on the brain by this chemical.

The CHAIRMAN. Your report indicates that the molecular basis for dopamine repositors was cloned in 1993. What is the importance of that finding?

Dr. O'BRIEN. Well, that is extremely important from the perspective of developing new medications. As a matter of fact, all of the major receptors for these drugs have now been cloned, and so this means that we have much more efficient ways of finding chemical compounds that have similar structures or that will match these receptors, and thus we can screen large numbers. So this is a very, very important step in the development of medications.

The CHAIRMAN. By receptors—it was once explained to me by one of your colleagues at Yale, in speaking to a group of people, he said the receptors in the brain are not unlike the receptacles for electrical outlets in your home. He suggested that, as you try very hard to figure out ways in which to prevent your 6-year-old crawling toddler from sticking his or her fingers in those receptacles—you have little things that are put over top of those receptacles to keep people from putting their fingers in. If you can't connect something to the receptacle, you don't get the desired effect. In this case, the desired effect would be electrical current that runs out of that receptacle.

Are receptors that you are referring to in the brain—and I apologize for being so pedantic here—are they places within the brain where in order for the reaction that is sought—in this case, pleasure, euphoria—that there has to be some interaction between the drug that is consumed and that part of the brain, or is it merely that what is supposed to interface with that receptacle is prevented from interfacing with that receptacle, some other chemical that is naturally available in the brain? Which is it, or is it both?

Dr. O'BRIEN. Well, for different drugs, it is——

The CHAIRMAN. Let us stick with cocaine.

Dr. O'BRIEN. For cocaine, there is this reuptake mechanism that——

The CHAIRMAN. What do you mean by "reuptake?"

Dr. O'BRIEN. This is the mechanism that conserves dopamine. In normal brains, without cocaine present, dopamine is released by a nerve cell and it attaches to its receptor and it excites the nerve cell, and one of the functions is pleasure; it is also movement. There is a whole variety of things.

When cocaine is aboard, it keeps the nerve cell from turning this system off. So, in a sense, it goes on unchecked and gives too much euphoria too quickly. What we see here is where the cocaine attaches to this reuptake mechanism which has been cloned, and the idea is to find a drug—and this is one object for the research—to find a drug which would keep cocaine from getting on to this reuptake mechanism without interfering with it itself, so it would have to be a very specific drug.

But now that the mechanism has been cloned, we know the various compounds, the amino acids, involved in its structure. It can be much more readily worked with in the laboratory in order to find a very specific drug which would block cocaine, but not block normal functions.

The CHAIRMAN. As you point out, this dopamine hypothesis is but one of three key neurotransmitters; that is, for the sake of everyone

who will read this, the messengers that send signals from one nerve cell to another. It is one of three key neurotransmitters. Is there research on these other transmitters that may impact on cocaine addiction?

Dr. O'BRIEN. Very much so, and the beauty of this is that it is teaching us more and more about the brain, so that it will affect the other transmitters you are talking about, transmitters such as serotonin and norepinephrine, and there are even many others besides that. As we learn even more about them, we learn not only more about cocaine dependence, but we also learn more about the other dependencies, such as alcohol and nicotine, and also about mental illness, such as schizophrenia and depression.

This research all links together. It is very, very much interrelated, and that is why we don't really want to rob from one area to fund medication development because that would be false economy. If we are going to improve this situation, we have to actually add funds to the overall picture. Otherwise, it would be lopsided.

The CHAIRMAN. Do you want to follow up?

Dr. EARLEY. Senator, if I might, the analogy you gave for blocking the electrical outlet is very applicable to opiates because methadone and LAAM for treating opiate addiction does, in fact, block the electrical outlet, so that now the heroin can't do its job. It blocks the outlet without the activating the undesirable effects that we would see with heroin.

We don't really have, I believe, Chuck, quite that complete an understanding of cocaine and its action, and there is no specific receptor that we can block at this time. I think the committee as a whole would agree that these limits in our fundamental understanding of the mechanism of action of cocaine, and even of heroin beyond the receptors, is, in fact, a limiting factor for the design of new medications that might be effective.

Is that a fair statement?

Dr. O'BRIEN. That is absolutely true, but since you bring up the opiate receptor, if I might, there are two examples that demonstrate how this process of research on the basic mechanisms of the brain can lead to things which are practically of benefit.

One of them was, by coincidence, in yesterday's Washington Post. It is some studies that were done—actually, much of the work came out of our lab in Philadelphia where there has been evidence that alcohol affects the opiate system. Many people are very sensitive to this effect, so that when they drink alcohol they get euphoria by exciting the opioid system, the opiate receptors in the brain. So if you block the opiate receptor, you block some of their euphoria from alcohol.

To make a long story short, as the article says in yesterday's newspaper, this has become potentially a very important new treatment for alcoholism. In combination with psychotherapy, with the AA groups, the 12-step Programs, we are now improving significantly our success rates for alcohol, and it has been found not only by our lab in Philadelphia, but also other centers as well, including Yale, have been finding the same results.

Second, there is another study that we did in Philadelphia with probationers who had been released from Federal prison who had a history of opiate-related crimes. We got an agreement from the

Federal judges in Philadelphia to allow us to do an experiment with these probationers, and we randomly assigned them to either a drug called naltrexone that blocks the opiate receptor or a control group.

What we found at the end of 6 months was that the reincarceration rate because of criminal activity was half the control group and those who were randomly assigned to this new medication that blocks opiate receptors. So here is a perfect example of research, first of all, beginning with animal research and then human research, and now a practical application in the real world that reduces crime.

The CHAIRMAN. I yield to my friend from Utah.

Senator HATCH. Well, this is terrific to discuss this. I take it that you only have basically two antiaddictive medications, methadone and LAAM, I guess, that have been developed, although there are others in the process of development?

Dr. O'BRIEN. Yes, that is correct, for opiate dependence, and LAAM is the first example of a drug that has come out of the NIDA Medications Development Program. It has been approved by the FDA, and that will have a major impact on the treatment of opiate dependence because it will allow people to essentially lead a much more normal life and makes them feel much better than methadone.

Senator HATCH. How many other drugs are in the pipeline right now, antiaddictive drugs or medications or pharmacotherapies?

Dr. O'BRIEN. The number of drugs in the pipeline really depends on where you start the pipeline. There are a lot of medications that are at a very early stage, but for cocaine dependence, for example, there are clinical trials going on with about half a dozen compounds that I am aware of right now, but none of them are as far along that we can really predict how soon they might be, or whether or not they even will be successful. For opiate dependence, bupenorphine is in the pipeline, and that shows a lot of promise and I think that will be approved as still another treatment for opiate dependence.

Senator HATCH. That brings me to another question. Yes, Dr. Crout?

STATEMENT OF J. RICHARD CROUT

Dr. CROUT. I think it is fair to say, Senator, that there is no drug for cocaine that is comparable to any of the two or three that you have seen for opiate addiction.

Senator HATCH. I see. Now, the Federal bureaucracy, of course, is a substantial player in the development and approval of medications, and we hear many complaints about the amount of money and time it costs to get Federal approval to market new drugs.

It has been said that it takes 10 to 15 years to get through the safety and efficacy process, at a cost of somewhere between $125 and $500 million, and 4,000 misses to arrive at a marketable drug. In developing an antiaddictive drug, if that is going to be the cost, then, of course, there is a natural deterrent to companies getting into it, with the limited patient base that we have of, like you say, about half a million to a million heroin addicts. And about 2 million, or more, cocaine addicts.

What is your sense of the way the Federal approval system is working, and what recommendations do you have for making it work better?

Dr. EARLEY. Well, we believe from the testimony that we heard as a committee that the review and approval system at the Federal level, and also at the State level, is, in fact, one of the deterrents for industry becoming more active in this research and discovery process.

Senator HATCH. It almost has to be a blockbuster drug to get the research money back under these circumstances.

Dr. EARLEY. The market itself is limited, in the view of industry. There is no up-front assurance——

Senator HATCH. Wouldn't it be helpful if Senator Biden and I put together an Orphan Drug bill for addictive drugs? In other words, the Orphan Drug Program applies to special populations of less than 200,000, but if we put together an incentive bill similar to the Orphan Drug bill, Joe? When we first introduced that bill there were 8 orphan drugs and they weren't very exciting, but after we did the Orphan Drug bill in, I guess it was 1984, within a short time we had 60 or 70, and now over 200. Would something like that be helpful to this process?

Dr. EARLEY. A recommendation of that sort, in fact, very much as you describe it, is, so to speak, on the tip of our tongue. We expect to have such a recommendation in our second report.

Senator HATCH. Senator Biden has worked on this before and, frankly, we just said to each other I would be happy to help him and I think we could work together to maybe do something like this.

The CHAIRMAN. Gentlemen, you have already done something significant. In 1989, I introduced an Orphan Drug Act and the Labor Committee, with good reason, was skeptical about it. I want to say publicly, Senator, I am very anxious, under your leadership, to work to resurrect that idea that I floated back in 1989, and maybe with the academic and intellectual support of this group, if that is the conclusion they reach, we might be able to get something going.

Senator HATCH. I think if we could do that, it might be a step in the right direction. But, you know, an Orphan Drug bill is an Orphan Drug bill, so you have got to have it so it works and so the incentives are right.

The CHAIRMAN. I agree.

Senator HATCH. I believe Senator Biden and I can be creative enough, with the help of others in the Senate, to be able to come up with something like that, and I am going to challenge both staffs to get together and let us see what we can do. But this still doesn't negate the fact that the safety and efficacy process at FDA is out of whack. When it takes 10 to 15 years to get a drug through the process, you know there is something wrong.

There are 100 vacancies out there at that agency right now. It is not their fault. Part of the problem is we can't acquire the best scientists because of the money that the Government pays. Private industry is so much more lucrative to them than working in public health, but there are those who want to and we ought to encourage them.

When we passed user fees here 1½ years ago, the idea was to shorten that safety and efficacy time so it would bring down the cost of pharmaceuticals and medications. In the meantime, we have had people here in the Congress who I think demogogically have been attacking the pharmaceutical industry for making outrageous profits when, in fact, when you invest $369 million into a drug, which is the average of what it costs today now, to get that back you have got to sell billions of dollars in gross sales to be able to pay for it, and some people don't seem to understand.

I was concerned about it. I didn't mean to dwell too much on it, but Senator Biden and I will work together. I don't know anybody in the Congress who has worked harder to try and resolve drug problems than Senator Biden, and it is a thrill for me to be able to be his right-hand person and to work with him in this area, and I am going to do it. We need your help and we need a lot of good advice on how to do it.

Now, let me just ask a couple of other questions.

The CHAIRMAN. In nonmedical terms, that translates into I will sponsor whatever he proposes. [Laughter.]

Senator HATCH. You mean I will sponsor whatever you propose?

The CHAIRMAN. No, no. I will sponsor whatever you propose.

Senator HATCH. We will work together on it.

I take it that even with methadone and LAAM, and whatever other antiaddictive drugs you have, that you still need some element of assistance therapy, and that is also an area where we get into difficulty because there are a limited number of therapists who have experience in this area and those who do have not had a tremendously high success ratio without antiaddictive drugs. Is that correct?

Dr. EARLEY. Yes, and one of our recommendations is that a system be developed for training more people in this area, and that would be a component of our recommended comprehensive centers for the study of drug addiction. They are limited, and Chuck can give you more detail?

Senator HATCH. Dr. O'Brien? And, Herb, we would like to hear from you on this. Dr. O'Brien, did you want to say something on this?

Dr. O'BRIEN. Well, certainly, we are in great need of more training centers. This is an area which is, of course, one of our most important public health problems, and you find very little of it in medical school curricula, nursing school curricula, social work or psychology curricula. So we have to do more training of therapists.

Actually, when trained therapists are working with people with addictive disorders, our results with the medications and the psychotherapies that we have available are not that bad. I mean, I think that there is a bad reputation that they have because there is such a high relapse rate.

Senator HATCH. Well, that is why.

Dr. O'BRIEN. But this is a chronic disorder.

Senator HATCH. Sure.

Dr. O'BRIEN. It is much like arthritis or heart disease or any other chronic disorder. You don't cure people, but you put them back to work. You get them back functioning again, taking care of their families, paying taxes, but they still are considered in recov-

ery and they still need some kind of therapeutic contact. I don't consider that a treatment failure, but it is a person who is not cured.

Senator HATCH. It is very difficult to treat, therapeutically or otherwise, people suffering from cocaine and heroin addiction. I mean, that is a tough job, and I just want to get it across that it isn't a simple little "send them to the psychiatrist and you are going to solve this problem."

Herb, it is good to see you again.

STATEMENT OF HERBERT D. KLEBER

Dr. KLEBER. I apologize for being late. I had to give a lecture at a medical school in New York at 8 a.m., but I was able to make it down here.

Senator HATCH. Well, that is a very poor excuse when you consider that Senator Biden and I want to hear everything you have to say.

Dr. KLEBER. Well, thank you for inviting me and I am delighted to be here.

Methadone is an excellent example of why medication alone isn't adequate. There are a number of studies showing, for example, that in a good methadone program success rates may be as high as 90 percent in terms of people no longer using illicit drugs. In a poorly run methadone program, success rates may be lower than 30 to 40 percent. The drug is the same. Nothing has changed with the drug, but the dose at which it is given, the training of the staff, the morale of the clinic—all of these become critical in whether that medication is going to succeed in keeping people away from using illicit drugs.

So training is very important. Money has to be looked at, too. Many of these programs—if you look at the ads in newspapers, you will see ads for counselors, $20,000 a year, no experience needed, to treat some of the most difficult patients we have. Many of these staff know nothing but their own recovery. That is also not adequate as treatment gets more sophisticated. So we need better trained staff, better compensated staff, and better behavioral techniques. As we improve our medications, we also need to improve our nonpharmacologic ways of intervening with these patients.

Senator HATCH. Well, as you may know, I take a great interest in psychiatry, and some of my Democrat colleagues believe that that is because I probably could benefit from analysis.

The CHAIRMAN. We analyze you all the time.

Senator HATCH. They do; it is just that they are faulty in their analysis—that is the problem—where I am sure you would be much more accurate.

Let me just say, in your report—and this will be my last question, Senator Biden. I don't want to dominate this time. In your report, you suggest that several actions be taken that would involve reducing the dual authority over clinical research currently held by the Food and Drug Administration and the Drug Enforcement Administration by exempting certain research from applicable DEA regulations, as I read your report.

If Congress were to accept these recommendations of yours, what do we really gain by such an action, not only in time, but in other

benefits to getting new medications developed, and really what would we risk?

Dr. CROUT. There is an interesting and very difficult tangle of regulations between the Food and Drug Administration, the DEA, and actually the methadone regulations of HHS. Those regulations, the DEA regulations and the HHS regulations, are basically set up to prevent diversion, and when you apply those to the clinical research setting along with the Food and Drug Administration regulations, it becomes procedurally almost impossible to meet all the requirements of both, particularly if you add on the requirements of a protocol.

Regulations, for instance, may define when a dose can be given or when urine samples must be taken and this sort of thing. Well, can you then do a protocol that violates those regulations? In the committee's view, this evolved with a good intent, but without a broad, eclectic view of the impact everywhere, and so we now face having to cut through that.

The committee's view would be that the Food and Drug Administration regulations are really the foundation of regulations that cover clinical research and are adequate for the clinical research setting, and that the thing to cut through, then, is the maize of regulations that are aimed at preventing diversion because the research setting is, we think, a minimal risk setting from which diversion can occur.

I would add one final comment. Remember that States have counterpart regulations and they are proving to be now very difficult—you know, a further tangled web. For example, the LAAM study that NIDA sponsored could not be done in the State of California because of its own regulations, and NIDA is now running into an inability to market, to sell, LAAM because of State regulations.

So there is a real problem here that we have not untangled and we need to work on it and present it to you, but it is a real problem, sir.

Senator HATCH. Why don't you help us to untangle it because both Senator Biden and I take a tremendous interest in what you are talking about here today? This is a very important hearing. It is a lot more important than I think it is being given credit for being. But if you can establish here today what we should do, we just may be able to do some things that might be very helpful to you.

Dr. EARLEY. The committee examined the Federal regulatory process.

Senator HATCH. You like that better?

Dr. EARLEY. The FDA itself has a process for expediting review and approval in the case of lifesaving drugs, for example, and we feel that when promising drugs come along for treating addiction that they should be given special review within the bounds, of course——

Senator HATCH. Do you feel they are not doing that at this point?

Dr. EARLEY. Well, the only drug that has really been cleared all the way through for market recently—I believe I am correct—is LAAM, and they are very—"they" being the FDA, the DEA and the Medications Development Division of NIDA—they, rightly so, are

very proud of the fact that they worked closely together to bring this drug to approval at a rate that would never have occurred had there not been interagency cooperation. One of the recommendations that will be coming from our committee will be that a process be formalized for expediting review of promising medications in this area.

I should also point out that there is a separate Institute of Medicine committee that is involved specifically with studying the methadone regulations, and presumably recommendations will be forthcoming shortly from that committee.

Senator HATCH. Thank you.

The CHAIRMAN. Herb, you wanted to say something before the Senator has to go to his other hearing?

Dr. KLEBER. Yes. I am a great fan of the DEA when it is carrying out its functions in terms of trying to keep illicit drugs out of the country. I think in this area of research, it at times does much more harm than good and its tangled webs at times have a chilling effect on the willingness pharmaceutical companies and on the willingness of academic researchers to get engaged in this area. When they do get engaged, they often make it very difficult to carry out the research.

I think the risks of diversion are extraordinarily minute. I think the good that could be accrued by giving FDA more authority in this area prior to drug approval, instead of DEA, would be very beneficial in terms of promoting the whole drug development process.

Senator HATCH. Well, thank you all. I appreciate that, and I thank you, Mr. Chairman.

The CHAIRMAN. Thank you, and I will look forward to working with you. Maybe, as you pointed out a moment ago, if we could move relatively quickly—maybe even on the Crime bill, if we could come up with some language, which hopefully in the next 3 weeks we will be passing out of here, to deal with——

Senator HATCH. Why don't you help us come up with language you think might set this in order?

The CHAIRMAN. As it relates to the orphan drug idea.

Senator HATCH. Well, plus this issue of the overlap between DEA and FDA, and we could put that in the same context, and the conflicts between Federal preemption and 50 States setting different standards that make it difficult to get these medications to the people who need them.

The CHAIRMAN. That would be great if you can do that.

Senator HATCH. If you can.

The CHAIRMAN. I am not as optimistic about the timeframe, but obviously if you could do that, that would be useful to help us on that score.

Thank you, Senator, very much.

Senator HATCH. Thank you.

The CHAIRMAN. Folks, I have a number of very specific questions, and I know your time is limited and I will try to stick to the questions, but let me make one further statement as to the overview here.

Herb, you have been an incredible ally from the beginning. I realize I have been kind of a pain in the neck to all my colleagues,

and maybe I suffer from what most Americans do, and that is an unrealistic faith in the science of science, an unrealistic faith in the notion that the incredible capabilities that you all represent hold real promise to deal with a problem that I think is the single biggest and most serious domestic problem facing the United States of America, and that is drug addiction and the byproducts of it.

Dr. O'Brien, if I go into your city of Philadelphia, or I go into any city where all of you live and I ask a Republican mayor in New York City or a Democratic mayor in Philadelphia the following question, if there was only one thing I could do as a Federal Government person to help the economic development of your city and ensure jobs, what is the one thing you would have me do, not a single mayor I have ever spoken to has asked for economic assistance first. They say, if there is any one thing you could do, if you could change the drug problem in my city, you would have more economic growth in New York City and in Philadelphia and every other major city in the Nation than anything else you could do for me. Forget empowerment zones and direct funding for development; just help me deal with my drug problem. So, that is what I mean when I say this is of immense, immense importance to the economic well-being of this Nation.

One of the things that I think relates to why we have had so much more emphasis on dealing with diversion, Dr. Earley, is because there is an underlying, I think, subconscious mind set in America that there really isn't much we can do in the pharmacological area or in the area of medicines that is going to help this overall problem. So the biggest fear is diversion. No one says it that way, but that is the fact of life.

One of the reasons for this hearing, which will be the first in a long series of hearings I am going to have on this subject because I have been sort of in the wilderness on this for the last 5 years, is to begin to change the mind set. If there was a belief that there was even a remote prospect of indirectly impacting upon the ultimate problem, the ultimate antisocial behavior that results from these addictions, then you would see a drastic mind set change.

Look at what happened with AIDS. AIDS is a national epidemic, and no more or less than drug addiction is a national epidemic in America having phenomenal social consequences, as AIDS does. We saw a completely different mind set in how the Federal Government wished to go about—it was tortuous at arriving at it, and still evolving, but a completely different mind set. That sense of urgency, I think, has to be brought to bear on this issue, without overpromising.

What I am not looking for, Dr. Earley, is a confirmation of my prejudice that science holds keys that are unavailable to policymakers other than through science. I acknowledge that prejudice, but I am not looking for confirmation of that if that is not true.

So let me go back to deal with some of the very practical policy constraints that make it difficult for you all to do what you, in varying degrees of optimism and pessimism, believe is possible through pharmacotherapy in this whole area of drug addiction.

I spoke briefly about the dopamine hypothesis as one of the three key neurotransmitters, and you indicated that there is research on the other neurotransmitters. It seems clear from your committee's

report, then, that we need to bolster our commitment to the basic science in the drug addiction field. Still, it seems that we can't ignore the clinical research component, that phase of research where we try as many safe, promising medicines as we can on actual addicts in controlled clinical studies.

What role does the committee believe we ought to devote to these controlled clinical studies?

Dr. KLEBER. The problem is a really good controlled clinical study is expensive and takes a long time. It can take 2 to 3 years to do an adequate study. In a recent review of the literature that I did, there have been 30 different medications that have been proposed for cocaine, over 100 different papers published. Relatively few have been controlled clinical trials. Most have been open case report kinds of things.

There is no question that we need the controlled clinical trial. What we need even more at this juncture is something that can occur before you get to the controlled clinical trial, something that would be a way of screening these compounds prior to going into this expensive and lengthy procedure—maybe a 2-, or 3-month procedure in a laboratory, such as my colleague at Columbia, Dr. Marion Fischman, does where you give cocaine, you give a possible medication, and you see what effect that has. If it looks promising, then you go into the controlled clinical trial. There is no substitute for that, but if you did it on every promising medication, we would bankrupt NIDA. There needs to be some way of figuring out which drugs should get to that controlled clinical trial.

The CHAIRMAN. I think one area where the drug companies get a bad rap is on the cost of developing new medicines. I spent some time with two large drug companies to try to see for myself—not so much that I have the educational background or, in a broad sense, the scientific vocabulary to understand everything that they were saying to me, but I was amazed, as I spent 1½ days in the laboratories of two different large pharmaceutical companies, about, first of all—not talking about controlled substances now; I am just talking about all medicines and new attempts to deal with finding new medicines.

First of all, I was amazed at what optimism is generated as a consequence of phenomenal new breakthroughs in computer science and the ability to use computers in their research in creating models that are needed in order for their scientists to make judgments about merely the shapes of the receptors, the interaction, the drug you have to find, mainly focusing on cancer research in this particular case.

When I raised with these two companies the issue of controlled substances and research in that area, they were very frank with me. They said, look, we have got a target market that isn't all that big; the cost for us to recoup our investment after clinical trials which will be required to market any of this is large relative to the return, and there is also a stigma attached to being involved in this kind of research; we are not sure we want to be known as the company that deals with cocaine addiction or deals with heroin addiction or opiate addiction.

Now, I would like to ask a few questions in that context about the future steps you have all recommended. While I have several

specific questions, I would like to first get to an overview of the key findings of the report. You have told me that the research is, in fact, promising, but I would like to get your views on the key steps the Nation has to take to deliver this early promise.

First, and most generally, is it the right approach that we even have a Medications Development Division within the National Institute on Drug Abuse to lead this research? Is that in and of itself the best way to go, and if not, what is the alternative?

Dr. O'BRIEN. Clearly, Mr. Chairman, that is absolutely the right approach. We need a Medications Development Division. That is not to say that that becomes the entire thrust of the institute because, as I said before, this is just one part of the multipronged attack.

But it is very clear from the data on the treatment of addictions that the best results come from a combination of psychosocial treatment and medication, and you can show that with alcoholism, you can show that with nicotine, you can certainly show that with heroin, and we hope to show that with cocaine as soon as we find a drug that is reliably effective.

The CHAIRMAN. Dr. Crout?

Dr. CROUT. I would emphasize that I think it is a very important step. We met with a number of industry executives and they all said national leadership from NIDA at the technical level is absolutely essential here. I think you need only look at the Cancer Institute through the years and the interaction it has had with the industry in developing medications and the fruits of that. There are many, many anticancer drugs out there today that went through an interactive program between the Cancer Institute and the private sector.

The CHAIRMAN. Now, as it relates to addictions, I have attempted to speak to as many folks in the treatment field—and I was amazed, Dr. Kleber, to find out that what you had told me 5 years ago was so accurate. Like you have just cited for the record, ads saying $20,000, no experience needed for clinical study—the incredible number of people I have gone to, who, in fact, have no basis for being involved other than that they were recovering alcoholics or recovering addicts.

I am not suggesting they should be condemned for that at all, but it did not give me the sense that were I to have a son, daughter, mother, father, brother, sister or me in that circumstance that I would get much other than psychic feedback and reassurance that they are somebody who made it or is making it.

The people with whom I have spoken at some of the treatment facilities seem to have a disposition or reluctance about prescribing any drugs anyway. The idea that another medicine is a component of the holistic treatment of a patient—and maybe I am wrong; this is a question. Is there a predisposition against that in the treatment field?

Dr. KLEBER. There is no question that part of the lack of progress that has been made in the treatment of substance abuse has been an ideologic interference by well-meaning people who believe, however, that medication doesn't have a role, that any medication is simply a crutch. In some ways, it is unfortunate that the main medication for treating opiates is what we call an agonist,

methadone, because that sort of confirms the belief of many of these individuals that the only medications that you are going to get are those that have some connection with the same action as the drug you are trying to treat.

It is clear that you have a variety of addicts. Some of them don't need any medication at all. Some need an agonist, like methadone. Some need an antagonist, like naltrexone. You need a spectrum, and we as a field need to get over this hump that believes that somehow you are weak, you are inferior, if you use a medication, which includes psychiatric medications. Too many of these self-help groups discourage you from taking your lithium if you are a manic depressive, or discourage you from taking an antidepressant because, "it is a crutch." We owe that to the country as a field to get over that.

The CHAIRMAN. Dr. Crout and then Dr. O'Brien.

Dr. CROUT. You put your finger on one of the histories of therapeutics. I mean, I am old enough to remember in my medical school and intern days when the treatment of high blood pressure was considered by many physicians a bad thing. I was taught that you needed the high blood pressure to get the blood through those narrowed vessels. The notion that you dilate the vessels and let it go through easier came later, and it came because of a drug. The drug preceded understanding of the disease. The same history applies to, let us say, if you remember thorazine for schizophrenia and what an impact that made in the mental health field.

So, typically, the drug comes first and them medical attitudes change. So all I am saying is what you said is true, but so what? You have to move ahead anyway.

The CHAIRMAN. I understand.

Dr. O'Brien?

Dr. O'BRIEN. Mr. Chairman, I just wanted to point out that the attitude that you cite is accurate, as Dr. Kleber said, but it is much less of a problem today than it was 10 or 20 years ago. In fact, now, more and more, we find that the self-help movement, the 12 steps, Alcoholics Anonymous, for example, is working along with us. They have meetings within our hospital, without our treatment programs, where patients are getting all kinds of medications, and we even have representatives from these groups who participate in the teaching of medical students at the University of Pennsylvania and then the medical students go with them out to the groups in the community.

So we are working together because we have a lot to learn from them and I think they recognize now that they have something to gain from the medical association.

The CHAIRMAN. Well, I think that is extremely useful. One of you said earlier the idea that medical students and the teaching profession seems to spend not as—and I don't mean this as a criticism, just an observation—seems to spend less time on looking at this field than it does in many other areas. As a consequence, we end up with fewer and fewer, whether they are medical personnel who are M.D.'s or whether they are nurses or whether they are therapists.

It was one of Bill Bennett's big bugaboos. His point was that even if we had the willingness to invest in treatment regimes,

many of which work—and he is now making that argument more forcefully—for a whole range of reasons I will not go into, we don't have that many people out there who are qualified to absorb the monies we might spend in order to get the biggest bang for the buck. But I guess that is another area we should revisit.

We have not fully funded what we promised we would do. Would fully funding the Medications Development Division, in fact, be beneficial, or is there a need to change the operation in some way? What I am trying to get to is, is the failure to fully fund something that is wise on our part and we should wait until there are internal changes made, or is it fully capable of absorbing and usefully expending the fully-funded budget that was passed but not funded?

Dr. EARLEY. It seems to me, Senator, that how the additional funding is to be used is an important question to ask. Despite the importance of the Medications Development Division in coordinating and stimulating the development of medications, they can't do the whole job. There will have to be incentives for the academic research community and for industry to become more involved before I think we begin to reach the goals that we envision.

If additional funding or full funding were to be used in part to create this concept of the comprehensive research, training and treatment centers around the country, then my own view would be, and I think this would be shared by some members of the committee, that that would be money well spent.

The CHAIRMAN. Anyone else? Yes, Dr. Kleber?

Dr. KLEBER. I think that additional funds could be well utilized. I think there also needs to be some structural changes. One of the complaints I hear which didn't really emerge in our report, but I hear it all the time from people at Medications Development, is that they probably need their own peer review committee.

Right now, the grants that they can fund come from review committees that are from elsewhere institutions which don't always fully understand the needs of Medications Development, and yet they are bound by the priority scores that arise from that review committee. However, I am told that trying to get a whole new review committee is one of these very, very difficult attempts.

The CHAIRMAN. Why is it so difficult? Educate me. Why is it so difficult?

Dr. KLEBER. Apparently, an institution is limited in terms of the number of committees, and in order to get permission you need not simply the permission of the institute director, but I think it even has to go higher than the NIH Director. I think it may have to go either to the assistant secretary or even to the secretary, so that it is a very high-level approval needed for a relatively low-level kind of change. But I think it is that kind of improvement that may enable you, if you give additional funds, to target those funds more appropriately.

The CHAIRMAN. I think if that were the consensus of this committee, we could take care of that relatively quickly. I am not being facetious. I mean, I think that could be done.

Dr. Crout?

Dr. CROUT. One comment that we got from NIDA was they feel very much an imbalance between the amount of staff they have and the amount of money. So I think that if more money were

given there, it can't be envisioned as simply more grants that they dispense to the outside world with the same staff.

The CHAIRMAN. They would need more staff?

Dr. CROUT. They need to do some other things which take talented people.

The CHAIRMAN. That is my impression as well.

Did you have something you wanted to say, Dr. O'Brien?

Dr. O'BRIEN. Actually, it relates to the other two comments because, in fact, what has happened is that there is a 10-percent reduction in staff across the board in NIH. So, essentially, this means a hiring freeze at NIDA, which had already been reduced in staff when it changed from ADAMHA to NIH. So there is a serious problem with lack of staff, and I think that additional funding would somehow have to take that into consideration.

As I said before, it would also have to take into consideration the problem of the need for Medications Development to rest within the entire framework of the basic research and the clinical research at NIDA, and it would do no good for Medications Development were the committee to recommend simply to set aside additional money for Medications Development because it would be taken from other areas which are equally important, and even important to Medications Development, but outside of that division.

Dr. KLEBER. I think that is a very critical point. Medications Development is only going to keep proceeding if you have the basic research. If the committee says, well, instead of $35 million, we would like it to go to $60 million and take that $25 million from elsewhere in NIDA, you are not only robbing Peter to pay Paul, but you are probably making Paul's job much, much more difficult to carry out.

The CHAIRMAN. But if we, in fact, proposed a pure add-on—we did not take away from the basic research grants that are going on, but, in addition to that, increased the money that was available for medicines, that would be, in your collective view, a generally wise approach, depending obviously on how much money and the like, but it would be well spent? Would that be a sound investment, or would it be better to increase the money for the basic research?

Let us assume we were able to generate an additional $40 or $50 million. Where would you put it? Would you put it in the basic research or would you put it where we are discussing?

Dr. O'BRIEN. Mr. Chairman, if you put it into Medications Development, then they would allocate a certain amount of it to basic research, and so that would be the most useful way to do it. It would be flexible, and then depending on what comes out of basic research, then what is most promising, they could actually allocate some of that to clinical research as things develop.

The CHAIRMAN. Do you all agree with that?

Dr. KLEBER. Yes, I certainly would heartily support that.

The CHAIRMAN. Your report identifies the division's establishment of a Cocaine Treatment Discovery Program, as well as several specific strategies undertaken for the program. What are some of the key components or strategies of the Cocaine Treatment Discovery Program?

Dr. CROUT. I think the report was reporting what, in fact, NIDA did.

The CHAIRMAN. I see.

Dr. CROUT. They obviously need a program of that type. What we learned was that that program is not going well, and it is not going well in part because of a small input of compounds from the private sector. This led to then, well, why is this happening? It is happening in part because of the pricing agreement in CRADA's, we were told. It is happening in part because of some language in the screening agreements that permit public disclosure after 3 years. It is happening because of disinterest by the industry. It is happening for a whole bunch of reasons that we have some recommendations on.

Probably, the broader, more general conclusion we reached was that NIDA needs to be the central leader and develop an interactive arrangement with industry of the type that seems to occur, say, in the cancer field. Now, how do you get there? We are now into all of the incentives and disincentives for the private sector we would like to address in the second half of our report. NIDA obviously can't solve this on its own.

The CHAIRMAN. The report also points out that the division has built a solid network of researchers who can carry out the controlled scientific clinical trials we must have to actually determine if medicines are, in fact, promising treatments for drug addiction.

First, though, is the reason we must do clinical research in this field that we don't have models that predict whether the medicines will be effective on addicts?

Dr. KLEBER. You have this wonderful catch-22 situation. We don't know how predictive the models will be because we don't yet have an adequate treatment, so that once we get an adequate treatment and we then say here is how it behaved in that model, you then know that model worked. So we have models that we think will have some predictive capabilities as far as new medications, but until that medication is developed, you can never be sure, but there are certainly some models out there that look promising.

The CHAIRMAN. How do you get us out of the catch?

Dr. KLEBER. Dr. O'Brien had his hand up. [Laughter.]

Dr. O'BRIEN. Actually, we have a proposal. It is part of the report and it is actually the policy of the Medications Development Division, as well, which is to work with all of the promising compounds in an organized way as rapidly as possible to test them in clinical trials—a moderate size that are of adequate sample size to detect an effect. As soon as a drug is found or a medication is found that has a reliable effect, then that can be tested in various animal models to see which animal model is sensitive to this effect, and then many more new compounds can be screened through this animal model.

But as Herb says, right now we have a lot of animal models that look as though they might be useful, but they haven't yet been proven valid in clinical trials. So there really is a great need to do more clinical trials and they have to be controlled clinical trials, and that means developing more of these centers that Dr. Earley talked about.

The CHAIRMAN. Well, that is what I wanted to get next. The report suggests funding these centers to bolster the division's efforts.

You have indicated why they are important, but do you have an estimate of the total cost of these centers? Would the Federal Government bear the entire cost of these centers, or is there any possibility of their being shared costs?

Dr. EARLEY. Shared with whom?

The CHAIRMAN. That is what I am asking. I can't think of whom. The staff suggested something that I think is useful, but fanciful, with universities or other institutions, but is there any incentive for, for example, universities to share in the cost of these centers? Is there any incentive for anybody other than the Federal Government to share in the costs?

Dr. EARLEY. There may be incentives for industry to share in them if industry could be stimulated to take a more active role here, and this gets back to dealing with some of the existing disincentives. There are recommendations that will be coming, and it seems to me that there might be incentives for industry, as I say, to share in these centers.

We envision the model of the Comprehensive Cancer Center that is supported pretty much in its entirety by Federal funding through NIH. It is true that patients who are in clinical trials may, in fact, be supported by third-party carriers, since they are undergoing treatment, so there is a way of sharing. For the universities to share in this cost, I think, is very farfetched.

The CHAIRMAN. Yes, Dr. O'Brien?

Dr. O'BRIEN. I would just like to point out that although we certainly need more incentives to get industry involved, the staff of the NIDA Medications Development Division needs to be commended for the work that they have already done even in the absence of adequate incentives. At the basic research level, they have gotten industry support for screening literally hundreds of thousands of compounds for their activity at these receptors that we have been talking about and at this reuptake site. As a result of this, they have got drugs in the pipeline that have some early promise, so that is one way that industry has given support.

Another way that industry has given support is in some of the existing clinical trials that have been done at some of these clinical research programs that Medications Development has already set up. In these programs, we have had partial NIDA funding for some of the basic work there, but then the drug company has provided the medication and has provided technicians and some support, so there has been this marriage. We have a little bit of a model of it, and this has been done without the kind of incentives that our report has recommended and we will detail in the second report.

Dr. KLEBER. I think that there are two additional possibilities here, and we will certainly explore this more in our next report. One is if you think of the pollution credits that industries can trade, so that an electrical company in New York can trade—it can pollute a little more by buying or selling things with Connecticut, or trading these kinds of things. One possibility is that if industry invests in these centers as a partner with the Federal Government that they get a tax credit which could be traded.

So if a small biotechnology company wanted to invest in these centers and a tax credit doesn't do it much good because it doesn't make much money, it could trade that tax credit with a company

like the one that makes Prozac where such a tax credit would be enormously valuable, and thus generate that kind of partnership in developing these academic centers. Two, to echo what Dr. O'Brien has said, a number of companies have already begun, not just directly through NIDA but directly with universities, to fund trials for potential cocaine medications.

The CHAIRMAN. I have more questions than you have time, and I am just trying to figure out—I will keep you another 5 minutes or so—what to move to. I would like to ask—and your staffs are going to go, oh, my Lord, he is going to do it—whether I can submit some of these questions to you in writing. There is no urgency in the matter of days or a week, but it would be helpful. I must tell you I have about 20 questions in areas that I haven't begun to really spend much time on—the budget, regulations, private sector development, the role of drug treatment, and dealing with some of your specific recommendations, some questions that flow from them.

Dr. KLEBER. The IOM staff is terrific, Senator.

Dr. EARLEY. Well, Senator, we would welcome receiving those questions.

The CHAIRMAN. Well, I will do that.

Let me end with just one or two questions on the regulation of research and development of medicines. As I noted in this 1989 report that I referred to, we have to reform our regulatory scheme to speed up the development and delivery of these treatments. The report I authored offered several reforms to speed the FDA approval process, and I note that the institute's report reaches several of the same conclusions, principally that the means the Nation developed to hasten the development and availability of medicines to treat AIDS can and should be used for medicines to treat drug addiction. Both diseases have killed far too many Americans and the diseases are linked. As IV drug abuse has so spread HIV that causes AIDS, as a Nation we have to do much more to combat these diseases.

I would like you to describe the status and the promise of several of these FDA reforms and what they might bring: First, treatment IND, the Biden report, and now the Institute of Medicine Report, endorses this approach. Can you tell me about your view of this mechanism? As I understand it, the FDA has not used this procedure for medications to treat drug addictions. Is that correct, and if it is, what is the potential role in research to treat drug abuse of that treatment IND?

Dr. CROUT. The FDA has not used that because there, in fact, is no drug up for approval, or let us say at midstage in development where a treatment IND would be appropriate. Both this suggestion and the one for parallel track——

The CHAIRMAN. That is what I was about to ask you.

Dr. CROUT. Are on the books at FDA. It is simply that the agency hasn't spoken up and said these also apply to the drug abuse area. So I think that this is not a step really in a major way for the FDA to take. I don't think it is a major step in policy. It would add to the positive atmosphere for development if the commissioner would join in, along with others, in saying, yes, the weapons I have to help you, I am going to see they come your way.

The CHAIRMAN. Well, your committee recommends the use of a mechanism that was not included in my report, that being the accelerated approval program. First, could you describe that process for us—describe the accelerated approval program for the record?

Dr. CROUT. There is a procedure under which drugs at the end of Phase II, which is basically when efficacy is clear but the wider use and long-term safety has not been established—there is a procedure under which a drug at that point may be approved, and then after marketing the sponsor is required to conduct, then, a longer-term equivalent to a Phase III study.

The CHAIRMAN. But the threshold you have to reach is there is meaningful therapeutic benefit?

Dr. CROUT. That is right. The threshold is lower, the time limit is shorter. The tradeoff is that if this Phase III trial doesn't work, then the drug may be withdrawn by the agency, basically, without any of the usual procedures for drug withdrawal.

The CHAIRMAN. Now, is what you are telling me that there are not any pharmacotherapies that reach that threshold of being meaningfully therapeutic?

Dr. CROUT. Correct.

The CHAIRMAN. Well, I have, as I said, a number of other questions. I have trespassed on your time too much already. I would like to tell you what I plan on doing from here, in addition to submitting some questions to you and looking forward to the second report.

I am going to invite in some of the drug companies and seek their input and their responses to some of the suggestions that you have put forward that may accommodate their willingness to do more. Toward that end, if you all have any suggestions as to how, if you were sitting in my chair, you would structure such a hearing process, it would be very helpful to me.

Again, I want to make it clear for the record that I am not casting, nor did you, the drug companies in the role of the bad guys here. This is not an attempt to do anything other than find out on my part for this institution what are the legitimate concerns, needs and recommendations of the major drug companies.

Am I correct in saying that unless we get considerable involvement of the private sector in this area, whatever is promising out there is less promising? They are a major player, is that correct?

Dr. EARLEY. That is what we believe, yes.

The CHAIRMAN. I happen to believe that as well. I think it is unavoidable. I mean, absent creating something the Government never does well, a competing Federal company, with overwhelming and phenomenal investment, which I think would be a very serious mistake, they are needed to get into the process.

So to the extent that you are able to give us either in writing or just verbally communicate to me methods by which you would—and I know, Dr. Kleber, you have been through this hearing process 500 times, and the three of you have conducted, in effect, hearings on your own to garner information on which way to approach certain issues. I would be very grateful if you have any suggestions.

Dr. EARLEY. Senator, would it help if we extracted from our report, as well as from our thinking toward our next report, the

items that we believe are disincentives and the areas which could be made incentives for industry to get more involved?

The CHAIRMAN. Yes, it would be. We have done that already, but it would be nice to see from your perspective how you would characterize it. I realize this is asking a lot. You have all done so darned much already, but what would be very helpful to me, if, in effect, I could borrow your staff for a little bit, is if you were conducting these hearings, what kinds of questions would you craft? What would you want to know from, what would you want to ask of the industry? That truly would be very helpful, and hopefully it would be helpful to you.

So I would like to, in effect, enter into a little bit of a partnership here. I have, as you already know, an inordinately high regard for all of you individually and for the entire effort you have undertaken here at our request, and I don't want you to be bashful about suggesting anything to me.

If you want to talk about matters that relate to the criminal justice system, the Constitution or foreign policy, I feel very, very well qualified to know how to craft whatever questions are needed, although I am always able to learn more. But I really am out of my field here. I need help and, quite frankly, we all are out of our field up here. I know of no one in the Congress who is a bona fide expert, and few of us have the background and training that you as scientists have.

So I very much need help because I still intuitively believe that with the proper guidance from the scientific community, the Federal Government can play a very constructive role and, I would argue based on what I have read and been told by all of you in your report, essentially the role as a catalyst here. Absent leadership coming from NIDA and/or the Federal Government in setting priorities and making judgments, which you have all said to me and the companies have said to me, it is not going to move very far, or very fast, anyway.

So I really need help, and I think it is obvious the Nation needs to help. And this is not, as you have observed, a partisan issue. This is one of the few things where I think we have little or no partisan bickering. As you remember, Dr. Kleber, it is probably the only area, mainly because no one but you and I and a few others took it seriously, where we never got much opposition.

It was always in terms of budget, not in terms of philosophy, not in terms of approach, just in terms of budget. So I have to build a better case in order to be able to convince my colleagues that my initial predisposition to expend considerably more money in this area is a worthwhile investment and, I would argue, has the potential to deliver a bigger bang for the buck than almost anything we can do in the entire drug control and criminal justice system to deal with this problem.

Again, I am not looking for you all to provide us a silver bullet. I am not suggesting that there is going to be a, "medical cure" that you are going to come up with, "you" meaning the scientific community. I am not suggesting that, but I do think that there is a phenomenal—again, in terms of investment and return, this is potentially the highest payoff area for us.

I am dumb-founded, Dr. O'Brien—you and I mentioned this before—I am dumb-founded as a lay person by the strides that the medical field is making in terms of how the brain functions over the last 5, 6, 7 years. I am literally living proof of the strides that have been made in neurological surgery over the last 15 years, but I am absolutely dumb-founded at how little we know and how much progress we are beginning to make in our cognitive capabilities of connecting the dots here.

I will end with a story I think I told you, Dr. O'Brien, up in Philly. For the record, I have two cranial aneurysms and I had two craniotomies. After the first one, which was one that, as they say in your field, bled, they identified a second one. I am told that somewhere around 25 percent of all people who have one have a mirror aneurysm, which was not as immediately life-threatening, but they believed that they should take care of.

I will never forget the same teams months later doing the second operation. As I was rolling in, there was a wonderful anesthesiologist, not only extremely competent, but was a real boost—I mean, a great sense of humor, and it is something that you like to have available to you as they are rolling you in on that little dolly into that room.

We had been talking about—and I don't expect any of you to comment on this. I will get myself in trouble. You know, I have heard other doctors kid neurosurgeons about neurosurgeons having the biggest egos of anyone in the medical profession. That was not the case with my neurosurgeons, but they were kidding about that. The vascular surgeon and the neurosurgeon were joking about that.

The anesthesiologist leaned over to me as he was standing behind me as we got into the room and he said, you know, Joe, why neurosurgeons have the biggest egos? And I said no. He said, who else could open up someone's head, go into the brain to do something to make things better knowing as little as they know about how the brain functions? It takes a phenomenal ego to be able to do that. [Laughter.]

I looked at him and I said, doctor, that is not a whole hell of a lot of reassurance at this moment, and we laughed about it. But it is amazing to me the strides you all are starting to make and, as you pointed out, Dr. O'Brien, which I wanted to get into, but time does not permit, the article in the Washington Post, how we are finding—you all are finding that there are potential applications to therapies that you come up with that affect areas that you never anticipated.

I remember one of your colleagues at Yale, who will remain nameless, that I had before this committee, a fine man, said to me, describing the difference between cocaine and opiate addiction—he said cocaine is like a lightning storm in the brain. He said, I was riding home one day and I realized that, you know, for epileptics we use carbomazepine—is that the correct?

Dr. O'BRIEN. Carbomazepine.

The CHAIRMAN. Carbomazepine, and there are various trade names that are used that they give as a prophylactic to guys like me right after I had my craniotomies.

All of a sudden, he said, well, we don't know why this works, but it seems to work, and he did some research on using it with cocaine addicts. The point was he was trying to make the case to the committee that we don't know why some of the things work or don't work and why they affect the brain the way they do or don't.

But your point, Dr. O'Brien, was that this is the decade of the brain. I am sure that no one in America would think it is the decade of the brain coming from the mouth of a U.S. Senator because they think we are all brainless, I think, here, but I understand what you mean. It is, I think, exciting, and I also think that I am not sure we know the exact path of how we are going to get from here to there, but I am confident a decade from now that you all in the scientific and medical community are going to have moved us a long way further down the road toward having pharmacotherapies available to impact more positively than now on, in my view, the number one domestic problem facing the United States, and that is drug addiction.

So it is in that context that I want to continue to push this issue. Again, I am not looking for answers to reinforce my prejudices. I am looking for approaches from the scientific community that enhance the prospect that a dollar spent will, in fact, have a potential payback in this area.

So, again, I thank you, Mr. Chairman, for taking this on, and all of you for being here, and I look forward to all the extra work I made for your staff today and I thank them as well for all they have done, and the help. You will be, I hope, helping me in the next series of hearings.

Dr. EARLEY. Thank you for having us, Senator, and as our study moves forward, if you would find it useful, we would be pleased to be invited to come back.

The CHAIRMAN. Well, I am confident we will ask you back. As some of you know, unfortunately for you now, as they say, I know where you live and I will privately, as well as officially here, occasionally call and ask you to continue my education in this area.

Thanks again, folks. I really do appreciate it. We are adjourned.

[Whereupon, at 12:05 p.m., the committee was adjourned.]

○

BOSTON PUBLIC LIBRARY
3 9999 05982 993 5

ISBN 0-16-047671-2